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(54) Title: ANTIMICROBIAL AND ANTI-INFLAMMATORY ENDOVASCULAR (CARDIOVASCULAR) STENT

(57) Abstract: An antimicrobial and anti-inflammatory endovascular (cardiovascular) stent including base material for the stent and an incorporated antimicrobial agent for the treatment of diseased blood vessel in such way that the antimicrobial agent is slowly released into the disease blood vessel wall which is in direct contact with the stent to treat the blood vessel tissue or the plaque by both killing the disease-causing microbe(s) and relieving the inflammation. The stent can slowly release the antimicrobial and anti-inflammatory agent(s) directly to the diseased tissue or the plaque that is infected by microbes. Consequently, the inflammation is relieved by the anti-inflammatory agent and the inflammation causing microbes are controlled or killed by the antimicrobial agent.

ANTIMICROBIAL AND ANTI-INFLAMMATORY ENDOVASCULAR (CARDIOVASCULAR) STENT

1. Field Of The Invention

The present invention relates to an antimicrobial and anti-inflammatory endovascular (cardiovascular) stent comprising an endovascular (cardiovascular) stent, and an incorporated antimicrobial agent for the treatment of diseased blood vessel in such way that the antimicrobial agent is slowly released into the diseased blood vessel wall which is in direct contact with the stent to treat the blood vessel tissue or the plaque by both killing the disease causing microbe(s) and relieving the inflammation.

More particularly, the present invention relates to an antimicrobial and anti-inflammatory endovascular/cardiovascular stent that slowly releases the antimicrobial and anti-inflammatory agent(s) directly to the diseased tissue or the plaque that is infected by microbes. Consequently, the inflammation is relieved by the anti-inflammatory agent and the inflammation causing microbes are controlled or killed by the antimicrobial agent.

BACKGROUND OF THE INVENTION

Arterial plaques (atherosclerotic plaques or atheromatous lesions) are the thickenings in the coronary arteries. They develop early in life, progressing over a period of many years with phases of quiescence or even regression interspersed with periods of progression. Such coronary atheromatous lesions are commonly found in virtually all adults in the industrialized world although most persons never have signs or symptoms of heart disease. In others, however, atheromatous lesions intrude into the lumen of the coronary arteries and progressively impede blood flow to the myocardium, leading to the clinical syndromes of coronary heart disease.

Balloon angioplasty (i.e., opening up an artery by inflating a balloon advanced across a site of narrowing) is one of the most widely used treatments for heart and vascular disease. However, approximately 33% to 50% of patients treated by balloon angioplasty have renewed narrowing of the treated arteries due to restenosis within six months of the initial procedure. This complication is often serious enough to necessitate further interventions, and stents have increasingly been used to reduce the incidence of restenosis. Notwithstanding, stents often become overgrown by inflammatory restenosis tissue.

Stents are hollow cylindrical devices made of plastic or metal that are inserted into body passageways for the local management of compression, narrowing, or obstruction of the passageway. In the treatment of heart disease, stents are introduced in a narrow collapsed state, guided by a catheter across the blockage, and expanded into place, usually by a balloon to physically hold open the coronary artery. Often, stents allow passage of blood through the previously obstructed artery and can eliminate the need for invasive procedures, such as coronary artery bypass surgery. However, the stents themselves become obstructed due to restenosis 10% to 25 % of the time, less than six months after insertion.

The process of restenosis is partially due to thickening of the blood vessel wall secondary to vascular smooth muscle cell ("VSMC") proliferation, VSMC migration into the inner aspect of the blood vessel wall (intima), and extracellular matrix deposition. There are several interdependent mechanisms which can initiate restenosis and are involved in the final common pathway of the disorder; among the most important being damage to the endothelial lining of the vessel and VSMC changes. Normally endothelium acts as a barrier that separates the blood elements from the remainder of the vessel wall. Consequently, loss or damage to the endothelium, which occurs during angioplasty, atherectomy, or stent insertion, results in a cascade of events that lead to restenosis.

These plaques that occlude coronary arteries are usually associated with infectious microbes, such as *Chlamydia pneumonia* (Jackson IA et al., Am J Pathol 1997 May); *Streptococcus sanguis*; and *Porphyromonas gingivalis* (Herzberg, MC, and Weyer, MW, 150(5):1785-1790); Ann Periodontol 1998 July; 3(1):151-160). The untreated infection of a blood vessel causes localized chronic host tissue inflammation and immune responses at the infected area. Over time, the plaque builds up in bulk and, consequently, constricts the lumen of the blood vessel segment where the chronic infection occurs. In addition to the bacterial agents known to be involved in plaque formation, recent studies indicate that a common virus called *cylomegalovirus* (CMV) may play a role in restenosis. (Zhou YF, Leon MB, Waclawiw MA, et. al., N Eng. J Med. 1996,335:624-30).

Systemic infusion of antibiotic compounds has also been recently suggested as a means to treat atherosclerotic plaques. However, because of the requirement of high dosage over a long treatment period, systemic infusion of antibiotic compounds for the treatment of these plaques may cause many unforeseen adverse effects. This is particularly true in the treatment of CMV, as the compounds most commonly used against this virus, gancyclovir, foscarnet, and combinations thereof are highly toxic and are typically only to be used to treat life threatening infections. Furthermore, development of resistance is common with systemic therapies, such that the drugs become progressively less effective and the disease progresses sooner.

SUMMARY OF THE INVENTION

It is well known that the conventional use of PTCA has very limited, long-term effectiveness to treat atherosclerotic plaques. Approximately 30% of patients have restenosis within 2 to 3 years. By treating the plaque area with indwelling antimicrobial stent(s) after a PTCA (percutaneous transluminal coronary angioplasty) procedure or open-heart procedure, the microbe(s) that has caused the original plaque is destroyed by the antimicrobial agents. Therefore, restenosis (i.e., renarrowing of

the arteries) is prevented. With the presence of an optional anti-inflammatory agent, the inflamed tissue is subdued more rapidly.

In this invention, an antimicrobial and anti-inflammatory vascular stent comprises vascular stent base material; and an incorporated antimicrobial and anti-inflammatory agent for the treatment of diseased blood vessels. It has three functions, i.e., the immediate mechanical support to maintain the patency of the treated blood vessel to allow normal blood flow through the lumen of the diseased blood vessel, the slow release of the antimicrobial agent(s) to kill the infectious microbes, and relieving the inflammation to prevent the renarrowing of the treated blood vessel.

The vascular stent base material can consist of metal alloy, polymer, ceramic or a combination of these materials. The physical form could be a "solid-wall" tube, porous tube, a tube of chick-wire structure, a spring-like coil or a combination thereof. The critical function of the stent is to keep the patency of the blood vessel, i.e. to allow normal or near-normal flow rate of blood at the treatment site of the vessel.

The incorporated antimicrobial agent is released from the stent by dissolution of the agent from the coating or matrix of the stent, hydrolysis and/or enzymatic digestion of the stent material, and a combination of the two mechanisms. The agent can be selected from groups of disinfectants, antiseptics, antibiotics, antimicrobial polymers, and combinations, co-polymers or blends of these compounds.

The device is directly placed in the lumen at the segment of the balloon-dilated blood vessel. Alternatively, it is placed in the lumen of a bypass vessel during a bypass surgery.

DETAILED DESCRIPTION OF THE, INVENTION

The antimicrobial and anti-inflammatory vascular stent of the present invention comprises vascular stent base material; an incorporated antimicrobial agent for the treatment of the narrowing of blood vessels and an incorporated anti-inflammatory agent to subdue the inflamed tissue.

The present invention is superior in many ways to the methods of prior art. The vascular stent on the market is intended to keep the patency of the blood vessel. It does not address the cause of the plaque formation and growth. Because the plaque's growth is not controlled, it can overcome the stent's function at the two ends and/or throughout the stent. That is if the stent is a durable, "solid-wall" tube, the plaque will build up and constrict the blood flow at the ends of the stent. Should the stent be of spring-like coil or "chicken-wire" like structure, the plaque's in-growth between the "wires" will also constrict the blood flow. In all cases, restenosis occurs and the patient will require an open-heart, by-pass surgery.

The antimicrobial vascular and anti-inflammation stent has three functions, i.e., the immediate or long-term mechanical support to maintain the patency of the treated blood vessel to allow normal blood flow through the lumen of the diseased blood vessel; the slow release of an anti-inflammatory agent to subdue the inflamed tissue, and the slow release of the antimicrobial agent(s) to control or kill the infectious microbes residing in the plaque. Because the plaque's growth is stopped, it prevents the future renarrowing of the stented blood vessel.

The antimicrobial vascular stent base material consists of metal, alloy, polymer, ceramic combinations, co-polymers or blends of these compounds. The physical form could be a "solid-wall" tube, a porous tube, a tube-like structure made of chick-wire like material, a spring-like coil, or a combination of them. The critical physical function of the stent is to keep the patency of the blood vessel, i.e. to allow normal or near-normal flow rate of blood at the treatment site of the vessel.

The stent can be constructed out of any of the traditional stent construction materials. Traditional stent materials include metals, alloys, polymers, glasses, ceramics.

The alloys include Nitinol, stainless steel carbide steel and other alloys made of two or more metals. The metals used to manufacture alloys include aluminum,

antimony, beryllium, carbon, cesium, chromium, cobalt, copper, gadolinium, gallium, gold, hafnium, indium, iridium, iron, lead, lithium, magnesium, manganese, molybdenum, nickel, niobium, osmium, palladium, platinum, polonium potassium, rhenium, rhodium, ruthenium, silver, sodium, tantalum, tin, titanium, tungsten, vanadium, yttrium, zinc, and zirconium.

The polymers include chemically synthetic polymers, natural polymers, modified natural polymers, genetically engineered polymers, and combinations, co-polymers or blends of these compounds. Examples of suitable polymers include Teflon, nylon, ethylene vinyl acetate, silicone, polyacenaphthalene, polyacetals, polyacetylene, polyacrylamide, polyacrylates, polyacrylonitrile, poly(alkylene glycols), poly(alkyl methacrylates), polyamic acid, polyamide-imide, polyamides, polybutadiene, polycarbonate, polychloroprene, polyesters, polyethers, polyethylene, polyethylene oxide, polyisobutylene, polyisoprene, polysulfones, polystyrene, poly(methyl methacrylate), poly(olefins), polypropylene, polysulfonamides, polysulfides, polytetrafluoroethylene, polyurethanes, poly(vinyl acetate), poly(vinyl alcohol), poly(vinyl amine), poly(vinylbutyral), poly(vinyl carbazole), poly(vinyl chloride), poly(vinyl fluoride), poly(vinyl formal), poly(vinylidene chloride), poly(vinyl isobutyl ether) poly(4-vinyl pyridine), poly(vinyl pyrrolidine), poly(vinyl stearate), copolymers, blends and combinations.

Biodegradable materials include polyacids, such as poly(3-hydroxybutyrate-3-hydroxyvalerate), poly (amino acids), polycaprolactone, poly-epsilon-caprolactone, polyesterbased biodegradable materials, poly(aminocaproic acid), polyanhydrides, polyorthoesters, polypeptides, such as polylysine, polyglycolic acids, polylactic acids, genetically engineered proteins, genetically engineered polysaccharides, genetically engineered DNAs and RNAS, copolymers, blends and combinations.

The ceramics include glass ceramics, ceramics made of base metals in the chemical compositions of borides, carbides, nitrides, oxides, and silicides, and

combinations, or blends of these compounds. The incorporated antimicrobial agent is released from the stent base material by dissolution of the agent from the coating or matrix of the stent material hydrolysis and/or enzymatic digestion of the stent material and a combination of the two mechanisms. The antimicrobial agents include disinfectants, antiseptics, antibiotics, antimicrobial polymers, and combinations, co-polymers or blends of these compounds.

The stent material may be coated with the pharmacologic compounds either directly or the compounds may be incorporated into a polymer coating on the stent material. Local delivery of drug(s) using stents is known by three methods: (1) directly coating the stent wires with a drug or a drug-polymer combination (Bailey et al., Circulation 82:III-541 (1990); Cavendar et al., Circulation 82:III-541 (1990)); (2) incorporating a drug into a stent that was constructed not of metal but of a biodegradable polymer (Murphy et al., J. Invasive Cardiol. 3:144-148 (1991)); and (3) a polymer sheath around the stent (U.S. Patent No. 5,383,928). Most investigators and stent companies have focused their efforts on directly coating the metal stent wires with a polymer. This polymer is usually placed directly on the stent (e.g., by dipping the stent in soluble polymer) or is covalently bound to the metal. The polymer is bonded to or contains the effective compound. Most coated stents currently under development use the anticoagulant, heparin, as their active agent. One of the more effective polymer coatings for stents is Biogold (van der Giessen et al., Circulation 82: III-542 (1990)).

If a polymer coating or sheath is used to coat the stent, both biodegradable and non-degradable polymers may be used. The polymer is selected depending on the drug selected, the polymer's compatibility with a subject and the ultimate pharmacologic effect desired. For example, if the effect need only last a short period, a thin polymer can be used with a limited amount of drug capable of diffusing from the polymer into the arterial wall or lumen. Alternatively, only the layer closest to the

body fluid would contain the drug. Another alternative would be to use a polymer that is biodegradable over a short period of time. Naturally, the opposite characteristics would be selected for a desired prolonged release. The characteristics of the particular polymer for these purposes is well known to the skilled artisan or can be determined by reference to standard references, e.g., Biodegradable Polymers as Drug Delivery Systems, R. Langer and M. Chasin, Eds., Marcel Dekker Inc., New York, N.Y., USA (1990); Engleberg and Kohn, "Physico-mechanical properties of degradable polymers used in medical applications: a comparative study," Biomaterials 12:292-304 (1991); Controlled Release Delivery Systems, T. J. Roseman and S. D. Mansdorf, Eds., Marcel Dekker Inc., New York, N.Y., USA (1983); and "Controlled Release Technology, Pharmaceutical Applications, ACS Symposium Series, Vol. 348, P. I. Lee and W. R. Good, Eds., American Chemical Society, Washington, D.C., USA (1987). Furthermore, a polymer may be chosen so that the breakdown products of the polymer have either an antimicrobial or an anti-inflammatory effect.

Antimicrobial agents are selective inhibitors of DNA, protein and cell wall metabolic pathways unique to susceptible organisms. Therapeutic success is achieved when the drug favorably affects the balance between microbial virulence and host resistance. This will occur if the drug is active against the infecting organism; an effective drug level is achieved at the site of infection; and host resistance is not compromised.

Effective prescription of antimicrobial therapy requires an accurate diagnosis and a decision on the need for antimicrobial therapy. An empirical assessment of likely invective organisms (based on the site and severity of infection, the patient's immunocompetence and a knowledge of local infection patterns) should be followed by a microbiological diagnosis and sensitivity testing whenever possible. Furthermore, many infections do not require, or are not susceptible to, specific

antimicrobial therapy. Unnecessary therapy is expensive and may result in adverse drug reactions and contribute to the problem of antibiotic resistance.

The choice of antimicrobial agent is based on known or likely invective organisms, site of infection, the immune status of the patient and renal and hepatic function. Single drug therapy using a narrow-spectrum agent is optimal and carries the least risk of superinfection and development of resistance. The use of multiple antibiotics is indicated only for short-term, empiric, broad-spectrum cover for serious infections or to minimize the risk of development of antibiotic resistance during therapy.

The antimicrobial compound is selected from the group consisting of antibacterial compounds, antifungal compounds, antiviral compounds, and antiprotozoal compounds.

Antibacterial compounds are those compounds which are destructive to or prevent the growth of bacteria. Both synthetic and antibiotic antibacterial compounds are suitable for use in the present invention. By antibiotic it is meant to include soluble substances derived from a mold or bacteria that inhibit or prevent the growth of other microorganisms. By synthetic, it is meant those antibacterial compounds artificially synthesized, rather than extracted or derived from a mold or bacteria.

Suitable antibiotic antibacterial compounds include aminoglycosides, amphenicols, ansamycins, ß-Lactams, lincosamides, macrolides, polypeptides, and tetracyclines. While not fitting neatly into one of the above classifications, other antibiotic antibacterial compounds such as cycloserine, mupirocin, and tuberin may also be suitable for use in the present invention.

Aminoglycosides are antibiotics whose structure contains amino sugars attached to an aminocyclitol ring (hexose nucleus) by glycosidic bonds. Aminoglycoside antibiotics are derived from various species of *streptomycin* and

micromonospora or are produced synthetically. They act by inhibiting protein synthesis, chiefly by binding to the 30S ribosomal subunits.

Amphenicols are broad-spectrum, mainly bacteriostatic antibiotics, active against a wide range of Gram-negative bacilli (but not *Pseudomonas),* staphylococci, streptococci, *Haemophilus* species, anaerobes and rickettsia, but ineffective against chlamydia and mycoplasma. Because of their potential to cause a plastic anemia, they should be reserved for severe infections caused by susceptible organisms.

ß-lactam compounds contain a four-membered ring with an amide nitrogen and a keto group. This configuration includes bacteriostatic, cell-wall inhibiting antibiotics, such as penicillins and cephalosporins; their analogs and derivatives, such as the penmen (or penman) compounds; clavulanic acids; ß-lactams; carbacephems; carbapenems; cephamycins; and monobactams. They are substrates for and may act as inhibitors of bacterial beta-lactamases.

Carbapenems comprise a group of ß-lactam antibiotics in which the sulfur atom in the thiazolidine ring of the penicillin molecule is replaced by a carbon atom. Thienamycins are a subgroup of carbapenems which have a sulfur atom as the first constituent of the side chain.

Cephalosporins are a group of broad-spectrum antibiotics first isolated from the Mediterranean fungus acremonium (*cephalosporium acremonium*). They contain the ß-lactam moiety thia-azabicyclo-octenecarboxylic acid, also called 7-aminocephalosporanic acid.

Cepbamycins are a naturally produced family of ß-lactam cephalosporin-type antibiotics having a 7-methoxy group and possessing marked resistance to the action of ß-lactamases from gram-positive and gram-negative organisms.

Lincosamides include clindamycin and lincomycin. Clindamycin is a derivative of lincomycin, but is more potent. Its mechanism of action is similar to that

of erythromycin: it binds to the 50S ribosomal subunits, selectively inhibiting bacterial protein synthesis.

Macrolides are a group of antibiotics containing a macrocyclic lactone ring linked glycosidically to one or more sugar moieties. These antibiotics are produced by certain species of *streptomyces*. They often inhibit protein synthesis by binding to the 50s subunits of 70s ribosomes.

Polypepide antibiotics are those antibiotics whose structure contains one or more peptides, usually cyclic. They are generally effective against gram-positive bacteria and act by inhibiting peptidoglycan synthesis in bacterial cell walls.

Glycopeptide antibiotics are those antibiotics whose structure contains one or more cyclic peptides to which are attached one or more deoxy sugars in glycosidic linkage. They are generally effective against gram-positive bacteria and act by inhibiting peptidoglycan synthesis in bacterial cell walls. An example of a glycopeptide antibiotic is vancomycin.

Tetracycline antibiotics are broad-spectrum natural and semisynthetic antibiotics with a naphthalene structure obtained from various *streptomyces* species. The tetracyclines are predominantly bacteriostatic agents that inhibit bacterial protein synthesis by binding to 30S ribosomal subunits in susceptible organisms. With the exception of doxycycline and minocycline, tetracyclines inhibit protein synthesis from amino acids in the patient, an antianabolic effect reflected by raised blood urea levels. Thus, localized delivery by the stent of the present invention, rather than systemic administration, would be beneficial if and when tetracycline use is indicated.

Synthetic antibacterial compounds include diaminopyrimidines; nitrofurans; quinolones and their analogs; sulfonamides; and sulfones.

2-4-diaminopyrimidines, such as trimetboprim, act by blocking the action of bacterial dihydrofolate reductase which leads to inhibition of folate synthesis in susceptible microorganisms. Trimethoprim is increasingly being used on its own and

its efficacy compares well with that of co-trimoxazole, with the advantage of fewer adverse effects.

Nitrofurans are generally effective against both gram-positive and gram-negative bacteria. Examples include nitrofurazone and nitrofurantoin. Nitrofurantoin is widely used for long term suppression of bacterial growth.

Quinolones, such as the fluoroquinolones, are bactericidal and act by inhibiting DNA gyrase, interfering with reproduction of bacterial DNA.

The sulphonamides are usually bacteriostatic and arrest cell growth by inhibiting bacterial folic acid synthesis. They are effective against sensitive strains of gram-negative and gram-positive bacteria *Actinomyces, Nocardia and Plasmodia.* However, extensive clinical use over many years has resulted in a high level of resistance and current use is limited.

Antifungal compounds are those compounds which are antagonistic to fungi. They can either be fungistatic (growth-inhibiting) or fungicidal (destructive action). Both synthetic and antibiotic antifungal compounds are suitable for use in the present invention.

Suitable antibiotic antifungal compounds are typically polyenes. Additionally, while not fitting neatly into any given category, other antifungal compounds such as azaserine; griseofulvin; oligomycins; neomycin undecylenate; pyrrolnitrin; siccanin; tuberculin; and viridin may be suitable for use in the present invention.

The most commonly used polyene antifugal compound is Amphotericin B.

Synthetic antifungal compound, include allylamines; imidazoles; thiocarbamates; and triazoles. While not fitting neatly into any of the above classifications, additional suitable synthetic antifungal compounds also include acrisorcin; amorolfine; biphenamine; bromosalicylchoranilide; buclosamide; calcium propionate; chlorphenesin; ciclopirox; cloxyquin; coparaffinate; diamthazole dihydrochloride; exalamide; flucytosine; halethazole; hexetidine; loflucarban;

niufuratel; potassium iodide; propionic acid; pyrithione; salicylanilide; sodium propionate; sulbentine; tenonitrozole; triacetin; ujothion; undecylenic acid; and zinc propionate.

The azole derivatives suitable for use in this invention include the imidazoles (e.g., ketoconazole and miconazole) and the triazoles (e.g., itraconazole and fluconazole). They have a broad spectrum of activity against several dermatophytes, *Candida, Cryptococcus* and other fungi that cause deep-seated infections. The mechanism of action involves inhibition of the cytochrome P450 enzyme responsible for conversion of lanosterol to ergosterol, the major sterol of most fungal cell membranes. The drugs' affinity is, however, not specific for fungal cytochrome P450; there is cross-reactivity with mammalian P450 enzymes and this explains the potential interference with human steroid synthesis and the interaction with other hepatically metabolized drugs. They have a broad antimycotic spectrum of activity and vary in their cidal and static effects.

Antiviral compounds are compounds which are destructive to a virus or otherwise weaken or abolish its action. The most commonly used antiviral compounds are the nucleoside analogues. Additional suitable antiviral compounds include acemannan; acetylleucine monoethanolamine; amantadine; amidinomycin; delavirdine; foscarnet sodium; indinavir; interferon-α; interferon-ß; interferon-γ; kethoxal; lysozyme; methisazone; moroxydine; nevirapine; podophyllotoxin; ribavirin; rimantadine; ritonavir; squinavir; stallimycin; statolon; tromantadine; and xenazoic acid.

The nucleoside analogues either interfere with DNA synthesis of viruses (acyclovir, ganciclovir, and cidofovir), or they inhibit reverse transcriptase of retroviruses (zidovudine and didanosine). Acyclovir, guanosine analogue, is phosphorylated to the active triphosphate form after uptake into the cell. Thymidine kinase catalyses the initial phosphorylation; selective toxicity in infected cells is due

to the greater affinity of the drug for viral, compared with host, thymidine kinase. Acyclovir triphosphate inhibits viral DNA polymerase, and it also competes with cellular deoxyguanosine triphosphate for incorporation into the viral DNA, thus terminating viral DNA systhesis. Ganciclovir, a guanine analogue, is active in the triphosphate form to which it is converted in the host cell. Ganciclovir triphosphate is a selective inhibitor of viral DNA polymerase and it competes with deoxyguanosine triphosphate for incorporation into DNA, causing chain termination. Ganciclovir triphosphate is concentrated in CMV-infected cells to a level ten-fold that in uninfected cells. In vitro activity against CMV is 100-fold greater than that of acyclovir, and against Epstein-Barr virus (EBV), 10-fold greater. Activity against herpes simplex and varicella-zoster is equivalent to acyclovir. Systemic use of ganciclovir is limited by toxicity. Cidofavir is a nucleotide analogue that also inhibits DNA polymerase activity. Its long intracellular half-life may lend itself well to slow delivery via impregnated stent.

Foscarnet sodium (syn. Trisodium phosphonoformate) is an inorganic pyrophosphate analogue that causes selective inhibition of viral DNA polymerase and reverse transcriptase, with little effect on host cell enzymes.

If the restinosis-inducing microbe is suspected to be cytomegalovirus (CMV) the preferred antiviral compounds are ganciclovir, cidofovir, and foscarnet sodium.

Antiprotozal compounds are compounds which are destructive to a protozoa or otherwise weaken or abolish its action. Suitable antiprotozal compounds include those compounds having action against ameba, giardia, histomonas, leishmania, malaria, pneumocystis, toxoplasma, trichomonas, and trypanosoma.

The stent of the present invention is preferably further impregnated or otherwise treated with an anti-inflammatory compound. The anti-inflammatory compound assists in the prevention of restinosis by reduction of inflammation at the site of infection. Anti-inflammatory compounds are those compounds which reduce

inflammation by acting on body mechanism without directly antagonizing the causative agent; and are generally divided into two main groups, non-steroidal and steroidal.

Nonsteroidal anti-inflammatory compounds include aminoarylcarboxylic acid derivatives; arylacetic acid derivatives; arylbutyric acid derivatives; arylcarboxylic acids; arylpropionic acid derivative; (e.g., naproxen); pyrazoles; pyrazolones; salicylic acid derivatives (e.g., aspirin); and thiazinecarboxamides. While not fitting neatly into any of the above categories, other anti-inflammatory compounds such as ε-acetamidocaproic acid; s-adenosylmethionine; 3-amino-4-hydroxybutyric acid; amixetrine; bendazac; benzydamine; α-bisabolol; bucolome; difenpiramide; ditazol; emorfazone; fepradinol; guaiazulene; nabumetone; nimesulide; oxaceprol; paranuline; perisoxal; proquazone; superoxide dismutase; tenidap; and zileuton may be suitable for use in the present invention.

The therapeutic properties of all the non-steroidal anti-inflammatory agents (NSAIDs) are characteristic of the prototype, aspirin, namely: analgesic, antipyretic and anti-inflammatory, the latter providing the potential for greater symptomatic relief in pain and discomfort associated with inflammation. Most of the actions of NSAIDs are probably attributable to their ability to inhibit cyclo-oxygenase, the enzyme responsible for prostaglandin synthesis. NSAIDs other than aspirin have these major properties at usual therapeutic doses, whereas high doses of aspirin (which may be poorly tolerated) are needed for significant anti-inflammatory effect. However, aspirin may have considerable cost advantage over the other NSAIDs.

In choosing NSAIDs, several factors must be considered. The differences in tolerability and efficacy among the various NSAIDs available are sometimes considerable, but the major factor influencing choice of agent is likely to be the wide variation in individual patient response-- many patients not responding to, or intolerant of, one drug may well benefit from another. The main differences among

the NSAIDs are pharmacokinetic and in the incidence and type of unwanted effects. The elimination half-lives vary widely, being the longest for piroxicam (37-86 hours) and tenoxicam (42-78 hours). All the NSAIDs have been associated with dermatological, gastrointestinal, renal, hepatic, hematological and immunological adverse effects, but differences may be largely determined by individual susceptibility. Patients who are pseudoallergic to a particular NSAID are prone to exhibit cross-reactivity to other NSAIDs, including aspirin (and possibly to tartrazine). The concurrent administration of different NSAIDs is not advised, on pharmacokinetic and efficacy/toxicity grounds.

Steroidal anti-inflammatory compounds are glucocorticoids, steroid-like compounds capable of significantly affecting intermediary metabolism. Examples include cortisone; hydrocortisone; and prednisone.

After the dilation of the blood vessel segment with PTCA procedure, the device is directly placed in the lumen of the diseased segment of the blood vessel.

PREPARATION OF COMPOSITION

The following specific examples will illustrate several embodiments of the present invention. It will be appreciated that other examples will be apparent to those of ordinary skill in the art and that the invention is not limited to these specific illustrative examples.

EXAMPLE 1

A sterile, surgical steel, endovascular (cardiovascular) stent is aseptically dipped into a sterile solution of 20% benzalkonium chloride, 5% hydrocortisone, and 75% ethanol solution. Then the coated device is aseptically air dried for 30 minutes at room temperature. The finished product is aseptically packaged and ready to be shipped to hospital.

EXAMPLE 2

An endovascular (cardiovascular) stent is made of 1% hydrocortisone and 99% tributyltin methacrylate-methyl methacrylate polymer by injection molding. Then it is packaged and sterilized using 1.0 MRAD gamma-radiation. After placing it inside the blood vessel, the polymer that is slowly hydrolyzed releases antimicrobial $ClSnBu_3$ molecules into the contacting plaque to kill infectious microbes.

EXAMPLE 3

Compound 98% polylactide, 1% 5-fluorocytosin and 0.1% trisamcinolone is extruded through a 100 micron die into a coil form with a 5-mm O.D. The coil is then cut into various lengths, such as 5, 10, 15 mm. After balloon dilation per PTCA procedure, a 10-mm long coil is chosen and placed in the treated vessel. The anti-microbial agent is slowly released from the stent as polylactide is gradually hydrolyzed over a period of 2 to 4 months.

EXAMPLE 4

A commercially available sterile endovascular (cardiovascular) stent is aseptically dipped into a solution of 50% Tecoflex, 45% THF and 5% nalidixic acid. The coated stent that is then aseptically dried in sterile air is packaged for either inventory or for shipment to hospital. The finished product is used to keep the treated blood vessel patent according to manufacturer's instruction for use.

What is claimed is:

1. An endovascular (cardiovascular) stent comprising:

(a) stent material; and

(b) an antimicrobial agent.

2. The stent of Claim 1 wherein the stent material is selected from the group consisting of polymers, metals, ceramics, shape-memory materials, bio-polymers, bio-degradable materials, combinations, blends and composites.

3. The stent of Claim 1 wherein the antimicrobial agent is covalently or ionically linked to the stent material, physically trapped throughout the stent, in a coating on the surface of the stent, and/or in the form of a base unit of a polymeric stent material.

4. The stent of Claim 1 wherein the antimicrobial agent is selected from the group consisting of anti-bacterial agents, anti-fungal agents, anti-viral agents, and combinations thereof.

5. The stent of Claim 1, further comprising an anti-inflammatory agent.

6. The stent of Claim 5, wherein said anti-inflammatory agent is covalently or ionically linked to the stent material, physically trapped throughout the stent, in a coating on the surface of the stent, and/or in the form of a base unit of a polymeric stent material.

7. The stent of Claim 5, wherein said anti-inflammatory agent is selected from the group consisting of anti-inflammatory enzymes, salicylates, steroids, sulfonamides, anti-viral agents, and anti-metabolites, and combinations thereof.

8. The stent of Claim 2 wherein the polymers or plastics include Teflon, nylon, ethylene vinyl acetate, silicone, polyacenaphthalene, polyacetals, polyacetylene, polyacrylamide, polyacrylates, polyacrylonitrile, poly(alkylene glycols), poly(alkyl methacrylates), polyamic acid, polyamide-imide, polyamides, polybutadiene, polycarbonate, polychloroprene, polyesters, polyethers, polyethylene,

polyethylene oxide, polyisobutylene, polyisoprene, polysulfones, polystyrene, poly(methyl methacrylate), poly(olefins), polypropylene, polysulfonamides, polysulfides, polytetrafluoroethylene, polyurethanes, poly(vinyl acetate), poly(vinyl alcohol), poly(vinylbutyral), poly(vinyl carbazole,) poly(vinyl chloride), poly(vinyl fluoride), poly(vinyl formal), poly(vinylidene chloride), poly(vinyl isobutyl ether) poly(4-vinyl pyridine), poly(vinyl pyrrolidone), poly(vinyl stearate), copolymers, blends and combinations thereof.

9. The stent of Claim 2 wherein the metals include aluminum, antimony, beryllium, carbon, cesium, chromium, cobalt, copper, gadolinium, gallium, gold, hafnium, indium, iridium, iron, lead, lithium, magnesium, manganese, molybdenum, nickel, niobium, osmium, palladium platinum, polonium, potassium, rhenium, rhodium ruthenium, silver, sodium, tantalum, tin, titanium, tungsten, vanadium, yttrium, zinc, zirconium and their alloys.

10. The stent of Claim 2 wherein the ceramics are selected from groups of borides, carbides, nitrides, oxides, and silicides and glass ceramics including glass and calcium phosphate-based materials.

11. The stent of Claim 2 wherein the shape-memory materials include Nitimol, a shape-memory nickel titanium alloy.

12. The stent of Claim 2 wherein the biopolymers include polysaccharides, mucopolysaccharides, proteins, lipids, polynucleotides, co-polymers, combinations, and blends.

13. The stent of Claim 2 wherein the biodegradable materials include polyacids, such as poly(3-hydroxybutyrate-3-hydroxyvalerate), poly (amino acids), polycaprolactone, poly-epsilon-caprolactone, polyester-based biodegradable materials, poly(aminocaproic acid), polyanhydrides, polyorthoesters, polypepides, such as polylysine, polyglycolic acids, polylactic acids, genetically engineered proteins,

genetically engineered polysaccharides, genetically engineered DNAs and RNAs, copolymers, blends and combinations thereof.

14. A method of treating atherosclerotic plaques and atheromatous lesions using an endovascular (cardiovascular) stent comprising:

a) stent material; and

b) an antimicrobial agent.

15. The stent of Claim 14 wherein the stent material is selected from the group consisting of polymers, metals, ceramics, shape-memory materials, bio-polymers, bio-degradable materials, combinations, blends and composites.

16. The stent of Claim 14 wherein the antimicrobial agent is covalently or ionically linked to the stent material, physically trapped throughout the stent, in a coating on the surface of the stent, and/or in the form of a base unit of a polymeric stent material.

17. The stent of Claim 14 wherein the antimicrobial agent is selected from the group consisting of anti-bacterial agents, anti-fungal agents, anti-viral agents, and combinations thereof.

18. The stent of Claim 14, further comprising an anti-inflammatory agent.

19. The stent of Claim 18, wherein said anti-inflammatory agent is covalently or ionically linked to the stent material, physically trapped throughout the stent, in a coating on the surface of the stent, and/or in the form of a base unit of a polymeric stent material.

20. The stent of Claim 18, wherein said anti-inflammatory agent is selected from the group consisting of anti-inflammatory enzymes, salicylates, steroids, sulfonamides, anti-viral agents, and anti-metabolites, and combinations thereof.

21. The stent of Claim 15 wherein the polymers or plastics include Teflon, nylon, ethylene vinyl acetate, silicone, polyacenaphthalene, polyacetals, polyacetylene, polyacrylamide, polyacrylates, polyacrylonitrile, poly(alkylene

glycols), poly(alkyl methacrylates), polyamic acid, polyamide-imide, polyamides, polybutadiene, polycarbonate, polychloroprene, polyesters, polyethers, polyethylene, polyethylene oxide, polyisobutylene, polyisoprene, polysulfones, polystyrene, poly(methyl methacrylate), poly(olefins), polypropylene, polysulfonamides, polysulfides, polytetrafluoroethylene, polyurethanes, poly(vinyl acetate), poly(vinyl alcohol), poly(vinylbutyral), poly(vinyl carbazole,) poly(vinyl chloride), poly(vinyl fluoride), poly(vinyl formal), poly(vinylidene chloride), poly(vinyl isobutyl ether) poly(4-vinyl pyridine), poly(vinyl pyrrolidone), poly(vinyl stearate), copolymers, blends and combinations thereof.

22. The stent of Claim 15 wherein the metals include aluminum, antimony, beryllium, carbon, cesium, chromium, cobalt, copper, gadolinium, gallium, gold, hafnium, indium, iridium, iron, lead, lithium, magnesium, manganese, molybdenum, nickel, niobium, osmium, palladium, platinum, polonium, potassium, rhenium, rhodium ruthenium, silver, sodium, tantalum, tin, titanium, tungsten, vanadium, yttrium, zinc, zirconium and their alloys.

23. The stent of Claim 15 wherein the ceramics are selected from groups of borides, carbides, nitrides, oxides, and silicides and glass ceramics including glass and calcium phosphate-based materials.

24. The stent of Claim 15 wherein the shape-memory materials include Nitimol, a shape-memory nickel titanium alloy.

25. The stent of Claim 15 wherein the biopolymers include polysaccharides, mucopolysaccharides, proteins, lipids, polynucleotides, co-polymers, combinations, and blends.

26. The stent of Claim 15 wherein the biodegradable materials include polyacids, such as poly(3-hydroxybutyrate-3-hydroxyvalerate), poly (amino acids), polycaprolactone, poly-epsilon-caprolactone, polyester-based biodegradable materials, poly(aminocaproic acid), polyanhydrides, polyorthoesters, polypepides, such as

polylysine, polyglycolic acids, polylactic acids, genetically engineered proteins, genetically engineered polysaccharides, genetically engineered DNAs and RNAs, copolymers, blends and combinations thereof.

INTERNATIONAL SEARCH REPORT

In' ıtional Application No
PCT/US 00/40979

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61L31/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61L A61F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 90 13332 A (CEDARS SINAI MEDICAL CENTER) 15 November 1990 (1990-11-15) page 5, line 10 -page 6, line 5 claims 1-3,5	1-22
X	US 5 869 127 A (ZHONG SHENG-PING) 9 February 1999 (1999-02-09) abstract column 7, line 18 - line 34 column 9, line 12 - line 23	1-3,5,6, 8-11, 14-16, 18,19, 21-24
A	WO 91 12779 A (MEDTRONIC INC) 5 September 1991 (1991-09-05) page 7, line 17 -page 10, line 18	1-3,5-7, 14-16, 18-20

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 January 2001	08/02/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Heck, G

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/40979

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 762 638 A (DOMB ABRAHAM J ET AL) 9 June 1998 (1998-06-09) column 1, line 15 - line 31 column 5, line 63 -column 6, line 32 -----	1,5,14, 18

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 14-26 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by surgery

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte tional Application No
PCT/US 00/40979

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